#23 Decl. w/ attach 3/7/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

HUANG et al.

Group Art Unit: 1651

Application No.: 08/882,499

Examiner: Marx

Filed: June 25, 1997

For: COMPOUNDS FOR THE SUPPRESSION . . .

* * * * *

August 24, 2000

SUBMISSION OF RULE 131 DECLARATION

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Please consider the Declaration under Rule 131 filed herewith and the following remarks.

REMARKS

Claims 5-7 are pending. Reconsideration is requested.

Claims 5-6 were rejected under the judicially created doctrine of obviousness-type double patenting over U.S. patent 5,663,209. A terminal disclaimer was filed on February 8, 2000. It is respectfully submitted that this overcomes the rejection.

Claims 5-7 were rejected under 35 USC § 102(e) as being anticipated by Sinnott et al. (U.S. Pat. No. 5,837,252). It is the Examiner's position that the complex formulation of Sinnott, comprising *Larrea tridentata* extracts, includes Mal 4, and further that the recitation "pharmaceutically acceptable derivatives thereof" might include the components of Sinnott's composition. On February 8, 2000, Applicants

submitted a Rule 131 Declaration that was deemed to be insufficient to overcome the rejection. The Examiner's attention is respectfully directed to the Declaration under Rule 131 filed herewith. The Declaration is signed by both inventors, and clearly states that the evidence presented therein was obtained in the U.S. before the priority date of Sinnott et al. The Declaration provides evidence establishing that viral transcription and accordingly viral growth is inhibited in both Herpes Simplex Virus (HSV) and Human Immunodeficiency Virus (HIV) by administering compounds according to the method of the invention. Item 4 details experimental data demonstrating the suppression of HSV, and item 5 details experimental data demonstrating the suppression of HIV. It is respectfully submitted that this evidence establishes that the invention was completed in the U.S. before the filing date of the Sinnott patent. Accordingly, withdrawal of the § 102(e) rejection is respectfully requested.

In view of the above, it is believed that the application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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By _____

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DECLARATION UNDER RULE 131

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

considered
m 8/10/00

Sir:

We, Ru-chih Huang and John N. Gnabre, do hereby declare and state:

1. We are the inventors on Patent Application No. 08/882,499, and we are familiar with the specification and prosecution history, including the Office Action issued September 24, 1999.

2. In the September 24, 1999 Office Action, the Examiner rejected pending claims 5-7 as being anticipated by U.S. Patent No. 5,837,252 issued to Sinnott et al. on November 17, 1998. The Sinnott et al. patent was filed on October 7, 1996, and claims priority to U.S. provisional application no. 60/020,946, filed July 1, 1996.

3. The invention described and claimed in Application No. 08/882,499 was made prior to July 1, 1996, as evidenced by the attached pages of laboratory notebooks, all dated prior to July 1, 1996. These data support claims 5-7 of the above-referenced application. In these laboratory notebook pages, two sets of experimental results were recorded, and are described below.

4. Exhibit A shows data demonstrating the suppression of HSV (Herpes Simplex Virus) Sp1-regulated α_4 transcription by 3'-O-methyl nordihydroguaiaretic acid (also known as "Mal.4" or "3-O-methyl NDGA"). These experiments were carried out in Dr. Huang's laboratory at Johns Hopkins University, Baltimore, MD, USA, prior to July 1, 1996. A plasmid pBRΔ380 carrying α_4 gene promoter (-380/+30) was first constructed. The suppression of α_4 promoter activity by Mal.4 was examined *in vitro*.

In the experiment to measure suppression of α_4 promoter activity by Mal.4, Mal.4 at 100 µg/ml and 130 µg/ml (and higher concentrations) was able to inhibit the α_4 promoter activity completely in an *in vitro* transcription system, as shown by the disappearance of the gel band representing the HSV α_4 transcript, indicated by the arrow in Figure A(1). The first gel ("H_2O") is the control, and the following gels show the effects of increasing amounts of Mal.4. These results were obtained and are dated prior to July 1, 1996.

5. Data from a further set of experiments on suppression of HIV promoter activity in Cos cells by a variety of methylated NDGAs is included as Exhibit B. These are compounds (including Mal.4) in which one or more -OH substituents of NDGA have been replaced by $-OCH_3$. These experiments show the inhibition of α_4 promoter driven Secreted Alkaline Phosphatase ("SEAP"), which correlates with inhibition of viral transcription and replication. The experiments were carried out using the method detailed in Exhibit B(1) for measuring SEAP.

Over the course of the work leading to the filing of the patent application, the designations of the compounds were slightly modified, and it is noted that the following correspondences between the abbreviations used in the data and the compounds disclosed in the present specification apply:

Mal.4 = 3-O-methyl NDGA

4-Me = 4-O-methyl NDGA

3',3"-diMe = 3,3'-di-O-methyl NDGA

4',4"-diMe = 4,4'-di-O-methyl NDGA

3',4'-diMe = 3,4-di-O-methyl NDGA

3',3",4'-triMe = 3,3',4-tri-O-methyl NDGA

3',4',4"-triMe = 3,4,4'-tri-O-methyl NDGA

The first set of SEAP results [Exhibit B(2)] shows the measurement of inhibition of SEAP at Mal.4 (3-O-methyl NDGA), in DMSO or in the form of Mal.4·$3Na^+$. The results are shown in

the two columns at the bottom of page 2 of Exhibit B(2). The left hand column shows the percent inhibition of SEAP by increasing concentrations of Mal.4 in DMSO, and the right hand column shows the percent inhibition of SEAP by increasing concentrations of Mal.4·3Na^+.

The second set of SEAP results [Exhibit B(3)] shows the measurement of inhibition of SEAP by Mal.4 plus seven methylated NDGA derivatives, 4-O-methyl NDGA, 3,3'-di-O-methyl NDGA, 4,4'-di-O-methyl NDGA, 3,4-di-O-methyl NDGA, 3,3',4-tri-O-methyl NDGA, 3,4,4'-tri-O-methyl NDGA and tetra-O-methyl NDGA (Compounds #1 - #7, respectively) at concentrations between 0 and 100 μM. The results are shown in graphical form in Figures B(1) and B(2).

6. The above studies were carried out in Dr. Huang's laboratory at Johns Hopkins University, Baltimore, MD, USA before July 1, 1996. These studies established for the first that transcription inhibitors such as NDGA derivatives can be used to suppress viral (HIV and HSV for example) promoter activities. Most significantly, the studies further showed that suppression of viral replication can be achieved by inhibition of viral transcription.

7. The results of the studies described above, the data of which are attached hereto in Exhibits A, B(1), B(2) and B(3) show that the invention described in U.S. application no.

08/882,499 was reduced to practice in the United States of America before July 1, 1996, the earliest priority date of U.S. Patent No. 5,837,252. These results clearly support claims 5-7 by demonstrating that NDGA derivatives can be used to suppress viral growth including HIV and HSV.

8. We declare further that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

By Ruchuan Chang Date Aug 18, 2000

By _____ Date August 21, 2000